REMARKS

The Claimed Invention

This invention provides methods of obtaining expression of a tumor suppressor gene or a suicide gene in a cell by contacting the cell with an adenoviral vector that has a deletion of all or part of the protein IX coding region. The deletion of the protein IX region from the adenoviral vector aids in the making of adenoviral preparations that are free of contaminating vectors that arise through recombination. Also provided by the invention are methods of using the vectors to treat a tumor in mammals.

Status of the Application

Claims 16-24 and 26-41 are pending in the above-referenced patent application and are currently under examination. Claim 16 has been amended to more specifically recite a method of treating a tumor. Support for the amendment to claim 16 is found throughout the specification as originally filed. No new matter has been introduced with the foregoing amendment. Reconsideration is respectfully requested.

First Rejection Under 35 U.S.C. § 112, First Paragraph

Claims 16-24, 26-31, 33, 35, 38 and 40 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled. In addition, claims 32, 34, 36-37, 39 and 41 were rejected under 35 U.S.C. § 112, first paragraph, as allegedly being nonenabled for a method for obtaining expression of a tumor suppressor gene or suicide protein in a cell *in vivo*. According to the Office Action, the gene therapy art at the time the invention was made was unpredictable, and the scope of the claims is overly broad. The Office Action also alleges that, while the specification is enabling for a method for obtaining expression of a tumor suppressor gene or suicide protein in a cell *in vitro*, it does not reasonably provide enablement for the method practiced *in vivo*. To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

The present invention provides methods of using vectors to obtain expression of a tumor suppressor gene or a suicide gene in a cell to treat a tumor in an animal. The vectors have a deletion of all or part of the protein IX coding region. The deletion of the protein IX region from the adenoviral vector aids in the making of adenoviral preparations that are free of contaminating vectors that arise through recombination.

The Office Action alleges that the present invention is nonenabled for a method for obtaining expression of a tumor suppressor gene or suicide protein in a cell *in vivo*. According to the Office Action, the scope of the claims is overly broad in that they read on treatment of any of thousands of different pathologies in animals or humans or potentially hundreds of different cancers. In response, Applicants have amended claim 16 to clarify that the method is a method of treating a tumor caused by the absence of a tumor suppressor gene or the presence of a pathologically mutated tumor suppressor gene. Amended claim 16 reads as follows:

> Claim 16. (currently amended): A method of treating a tumor in an animal or mammal caused by the absence of a tumor suppressor gene or the presence of a pathologically mutated tumor suppressor gene, the method comprising administering to the animal or mammal an effective amount of a recombinant adenovirus expression vector comprising: a) a partial or total deletion of a protein IX-encoding DNA sequence, and b) a gene encoding a foreign functional protein having a tumor suppressive function, under suitable conditions.

As amended, the method is clearly directed to treating a tumor caused by the absence of a tumor suppressor gene or the presence of a pathologically mutated tumor suppressor gene. Applicants respectfully direct the Examiner's attention to the attached Declaration of Daniel C. Maneval, Ph.D., filed pursuant to 37 C.F.R. § 1.132. In the Declaration, Dr. Maneval asserts "the restoration of p53 function in tumor cells by delivering a gene encoding p53 via a delivery system of the present invention would be expected to be useful in suppressing a wide range of tumor types. Similarly, the expression of anti-

tumor genes are effective in killing a broad range of tumor cells times...As such, one would expect that a broad range of cancer cells would be susceptible to killing by the expression of such anti-tumor genes." (*See,* Paragraph 11 of the Declaration.) As such, the scope of the claims is not overly broad.

The Office Action alleges that the present invention is nonenabled because the amount of guidance presented in the specification is insufficient for one of skill in the art to make and use the invention. In response, Applicants respectfully direct the Examiner's attention to the attached Declaration of Daniel C. Maneval, Ph.D., filed pursuant to 37 C.F.R. § 1.132. In the Declaration, Dr. Maneval asserts that the present invention is enabled by the specification, and that one of skill in the art could make and use the claimed invention based on information provided in the specification. According to Dr. Maneval, one of skill in the art would readily be able to make the adenoviral vectors of the present invention based on the information provided in the present specification, and carry out the steps necessary to administer such vectors to humans or other animals. According to Dr. Maneval, the present specification provides ample guidance for the design of suitable vectors, methods and locations of administration, appropriate dosages, and the like. More particularly, the specification provides, for example, a detailed description of suitable adenoviral vectors, including suitable promoters, for the use in expressing a gene of interest. Tumor suppressor and suicide genes useful in the present invention are described in the specification and include, for example, retinoblastoma, p16, p21, Wilm's tumor WT1 protein, mitosin, h-NUC, and colon carcinoma DCC protein (*see*, page 17, lines 16-29 of the specification). A working example demonstrating that recombinant adenoviruses expressing a tumor suppressor wild-type p53 can efficiently inhibit DNA synthesis and suppress the growth of a broad range of human tumor cell types, including clinical targets, is also provided in the specification as Experiment No. II (*see*, pages 32-45 of the specification).

The Examiner is concerned that the data using nude mice bearing Hep3B tumors is unclear as to how they relate to treatment of cancers in patients, and if the data

is recognized as being reasonably predictive of results which would be expected in patients. According to Dr. Maneval, "human tumor xenograft models are generally accepted in the scientific community as reasonably predictive of the efficacy of anti-cancer agents in human beings. The present specification provides in vivo data demonstrating the efficacy of the compositions of the present invention using two human xenograft tumor models, the Hep3B and H69 mouse models." (*See*, Paragraph 10 of the Declaration.) Dr. Maneval asserts "Hep3B and H69 are tumor cell lines which are used to establish tumors in animals and provide a model system for establishing therapeutic or pharmacological utility of a potential cancer treatment." The nude mice bearing Hep3B tumors were treated intratumorally and peritumorally with the vectors of the present invention (*see*, page 53, lines 30-31 bridging to page 54, lines 1-10 of the specification). In comparison with the control treatment, the vector containing the suicide gene resulted in smaller average tumor size, thus supporting a specific effect on tumor growth *in vivo*. Furthermore, Dr. Maneval declares the following:

> The specification also provides *in vitro* and ***in vivo*** results demonstrating activity of recombinant vectors which contain an anti-tumor gene. It is my belief that the specification provides data that demonstrates that the claimed methods can reduce tumor growth *in vivo*. Experiment II (pp. 32-45) describes an experiment in which the administration of an adenoviral vector encoding the p53 tumor suppressor protein was found to greatly reduce the growth of established tumors and significantly enhance survival times of tumor bearing animals. The last of the control adenovirus-treated animals died on day 83, while all five animals treated with a p53-expressing vector were still alive 130 days after tumor cell inoculation.

Dr. Maneval asserts that this experimental data, which is provided in the present specification, demonstrates that an adenovirus vector that expresses p53 was effective in greatly reducing the growth of established tumors and significantly enhancing survival times of animals having tumors. Clearly, the tumor suppressor protein p53 was

expressed in the tumor cells *in vivo* using the methods of the present invention. In another working example, Experiment No. III (*see*, pages 45-54 of the specification), the suicide gene TK is expressed in liver tumors in mice using the methods of the present invention. The data from Experiment Nos. II and III clearly show that the claimed methods are sufficiently supported by description in the specification so as to enable one of skill in the art to obtain expression of a tumor suppressor gene or suicide protein in a cell *in vivo*. As such, Applicants assert that one of skill in the art would ***not*** have had to practice undue and excessive experimentation in order to practice the claimed invention.

In addition, in their clinical trials, the Applicants demonstrated the operability of their methods for the delivery of the p53 gene in human cancer patients. A list of journal articles reporting the results of their clinical trials is provided in Table I below.

Table I

Authors/Citation	Therapeutic Agent	Route of Administration	Dosing Regimen
Wen, et al (2003) Cancer Gene Therapy 10:224-38	SCH 58500 (a replication deficient recombinant adenovirus expressing p53)	Intraperitoneal Instillation	"multiple cycles" of $7.5x10^{13}$ particles daily for five consecutive days alone and in combination with chemotherapy (gemcitabine)
Buller, et al. (2002) Cancer Gene Therapy 9(7):553-566	SCH 58500 (a replication deficient recombinant adenovirus expressing p53)	Intraperitoneal Instillation	Escalating doses of from $7.5x\ 10^{10}$ to $7.5\ x\ 10^{12}$; 2-3 doses up to $2.5x10^{13}$ particles per dose for three cycles; $7.5x10^{13}$ particles per day for five days for three weeks, week one alone and weeks 2 and 3 in combination with chemotherapy (carboplatin/paclitaxel)
Kuball, et al. (2002) J. Clin. Oncol. 20(4):957-965	SCH 58500 (a replication deficient recombinant adenovirus expressing p53)	Intratumor injection and intravesical instillation	Three dose levels; $7.5x10^{11}$; $7.5x\ 10^{12}$; $7.5x10^{13}$ particles per dose; single dose; in combination with Big CHAP formulant

Copies of each of the references listed in Table I are provided herein as Exhibit B for the Examiner's convenience. The clinical trials discussed in the references used:

1. a tumor suppressor gene, p 53
2. intravesical administration as the relevant route of administration
3. a protein IX deleted adenoviral vector gene delivery system

The trials clearly demonstrated that administration of a protein IX deleted adenoviral vector system comprising the p53 gene does result in specific transgene expression in tissues treated with the methods of the present invention (*see*, page 960, last paragraph bridging to page 961, Kuball *et al.*; page 559, last paragraph bridging to page 560, Buller *et al.*; and page 227, last paragraph bridging to page 228, and page 228, second paragraph, Wen *et al.*). In all three clinical trials, elevated RNA levels of transgenic p53 was observed in the target tissues. Thus, the data from Applicants' clinical trials clearly show that the claimed methods and present specification are enabled for one of skill in the art to obtain expression of a tumor suppressor gene or suicide protein in a cell *in vivo*.

The analysis of what constitutes an enabling disclosure is based on the Wands factors. Here, Applicants address two seminal issues of concern to the Examiner:

(1) the legal issue of the appropriate standard of review, and

(2) the factual issue of the level of skill of ordinarily skilled artisan.

Applicants believe that the following remarks considered in view of the above remarks, the attached information and Dr. Maneval's Declaration provide sufficient evidence to demonstrate that the present specification is sufficient to support the scope of the pending claims. Consequently, the inquiry is whether or not the skilled artisan would be able to employ the vectors of the present invention in their broadest scope without more teaching than that provided by the specification.

As the Examiner is aware, the level of the ordinarily skilled artisan employing recombinant viral vectors for therapeutic applications, *ex vivo* or *in vivo* is exceptionally high. The pending Office Action does not concede nor dispute the qualifications of the ordinarily skilled artisan, but questions rather the predictability of the art and that undue experimentation would be required. Whether or not undue experimentation would be required to practice the claimed invention is a matter of law

independent of the factual inquiry of the qualifications of the ordinarily skilled artisan.[1] *Enzo Biochem, Inc. v. Calgene* (CAFC, 1999). The qualifications of the ordinarily skilled artisan are a question of fact. Ibid. Applicants wish to provide additional information which demonstrates that the level of expertise in this field is exceptionally high.

Attached to this Response as Exhibit C is a printout of the summary of the pending RAC-approved Human Gene Transfer Protocols obtained from the National Institutes of Health (NIH) website (http://www4.od.nih.gov/oba/rac/clinicaltrial.htm). As can be seen from the extensive number of approved protocols, almost without exception all of these protocols have been performed by those having at least an M.D. degree at a major university teaching hospital or prominent clinical institution (*e.g.*, University of California, San Francisco Medical Center, University of Pennsylvania Medical Center, MD Anderson Cancer Center). The academic and professional backgrounds of these individuals is exceptional. Simply by way of illustration and specifically in relation to the present invention, there are at least five ongoing studies relating to gene therapy with tumor suppressor proteins or suicide proteins:

1. A Phase I clinical trial study of p53 gene therapy using adenovirus vector delivery to treat of non-small cell lung cancer at the MD Anderson Cancer Center under the direction of Dr. Jack Roth.
2. A Phase I clinical trial study of HSV-thymidine kinase gene therapy using adenovirus vector delivery to treat advanced CNS malignancy using adenovirus delivery at the University of Pennsylvania Medical Center under the direction of Dr. Stephen Eck.
3. A Phase I clinical trial study of p53 gene therapy using adenovirus vector delivery to treat locally advanced or recurrent adenocarcinoma of the prostate at the UCLA School of Medicine under the direction of Dr. Arie Belldegrun.

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[1] The CAFC states, "Whether undue experimentation would have been required to make and use an invention, and thus whether a disclosure is enabling under 35 U.S.C. § 112, ¶ 1, is a question of law that we review de novo, based on underlying factual inquiries that we review for clear error. See Johns Hopkins Univ. v. Cellpro, Inc., 152 F.3d 1342, 1354, 47 USPQ2d 1705, 1713 (Fed. Cir. 1998) (citing Wands, 858 F.2d at 736-37, 8 USPQ2d at 1402, 1404)."

4. A Phase I clinical trial study of p53 gene therapy using adenovirus delivery to treat breast cancer at the Fox Chase Cancer Center under the direction of Dr. Margaret von Mehren.
5. A Phase I clinical trial study of p53 gene therapy using adenovirus delivery to treat primary and metastatic malignant tumors of the liver using adenovirus vector delivery at the University of California, San Francisco Medical Center under the direction of Dr. Alan Venook.

A brief review of the status of these investigators provides a snapshot of the ordinarily skilled artisan in this field. Jack Roth, M.D. served as head of the Thoracic Oncology Section of the Surgery Branch of the National Cancer Institute and is currently Professor and Chairman of the Department of Thoracic and Cardiovascular Surgery at the University of Texas MD Anderson Cancer Center. Stephen L. Eck, M.D., Ph.D. is a researcher at the Institute for Human Gene Therapy at the University of Pennsylvania Medical Center. Arie Belldegrun, M.D., is the Chief of the Division of Urologic Oncology and Director of Urologic Research in the Department of Urology at the University of California, Los Angeles, a UCLA Professor of Urology, Clinical Director of the UCLA Prostate Disease Research Program, and Surgical Director of the UCLA Kidney Cancer Program. Margaret von Mehren is a clinical researcher at the Fox Chase Cancer Center. Alan Venook, M.D., is the Director of the Liver Tumor Treatment Group in the Division of Hematology and Oncology at the University of California San Francisco, the Chief of the Section of Gastrointestinal Oncology, and an Associate Professor of Clinical Medicine. Clearly, these individuals are not only highly qualified physicians but leaders in their field.

Therefore, Applicants believe that this information demonstrates that the "ordinarily skilled artisan" in the field of clinical gene therapy is a highly trained and specialized physician in an academic medical school at a major university possessing an exceptional academic background.

The Office Action alleges that gene therapy at the time the invention was made was unpredictable. In Dr. Maneval's expert opinion, gene therapy was enabled at

the time of the invention. In paragraph 8 of the Declaration, Dr. Maneval asserts that, "numerous FDA approved gene therapy clinical trials involving adenoviral vectors were underway at the time the invention was made. Additionally, there were numerous reports in the scientific literature regarding the clinical administration of recombinant adenoviral vectors encoding therapeutic transgenes to human beings. Therefore, one of skill in the art would have had knowledge of these reports and, combined with the teaching of the present specification, would have been able to employ the vectors of the present invention in the treatment of human cancers without undue experimentation."

The relevant art supports the therapeutic efficacy of gene therapy with tumor suppressor genes. For instance, see U.S. Patent No. 5,532,220, which issued on July 2, 1996, with an earliest priority date of July 16, 1990, more than ***3 years before the priority date of the present application***. The '220 patent issued with these claims:

> 1. A method of ***treating*** **mammalian cancer cells lacking endogenous wild-type *p53* protein**, comprising introducing a wild-type ***p53*** tumor suppressor gene encoding said endogenous wild-type ***p53*** protein into said mammalian cancer cells, whereby said mammalian cancer cells' neoplastic phenotype is suppressed.
>
> 2. A method of ***treating*** mammalian cancer cells lacking endogenous wild-type ***p53*** protein, comprising introducing into said mammalian cancer cells a wild-type ***p53*** tumor suppressor gene derived from the same mammalian species as said mammalian cancer cells, whereby said mammalian cancer cells' neoplastic phenotype is suppressed.
>
> 3. The method of claim 1 or 2, wherein the mammalian cancer cell having no endogenous wild-type ***p53*** protein lacks the wild-type ***p53*** tumor suppressor gene.
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> 4. The method of claim 1 or 2, wherein the mammalian cancer cell having no endogenous wild-type ***p53*** protein has a mutated ***p53*** tumor suppressor gene.
>
> 5. The method of claim 1 or 2, wherein the introduction of the wild-type ***p53*** tumor suppressor gene is by **retroviral infection.**

> 6. The method of claim 1 or 2, wherein the mammalian ***cancer cell*** is an osteosarcoma cell, lung carcinoma cell, lymphoma cell, leukemia cell, soft-tissue sarcoma cell, breast carcinoma cell, bladder carcinoma cell or prostate carcinoma cell.

See also claim 1 of U.S. Patent No. 6,143,727, which is drawn to the administration of p53 gene in conjunction with a skin specific promoter to treat skin cancer and is a divisional of an application with a priority date of November 1993. See also U.S. Patent No. 6,030,956, with an earliest priority date of Oct. 24, 1996 which claimed a vector composition comprising a p53 gene (claim 1) for use in cancer treatment with no limitation as to the type of cancer. See also U.S. Patent No. 6,338,962, with an earliest priority date of September 11, 1996. The '962 patent claims methods of treating bladder cancer by administering a p53 gene in a viral vector:

> 3. A method for ***treating*** **a cancer in a mammal**, said method comprising:
>
> a) introducing into a cancerous cell of said mammal a non-mammalian DNA virus the genome of which comprises a cancer-therapeutic gene selected from the group consisting of tumor necrosis factor, ***p53,*** thymidine kinase, diphtheria toxin chimeras, and cytosine deaminase; and
>
> b) maintaining the cell in said mammal under conditions such that said cancer-therapeutic gene is expressed.
>
> 4. The method of claim 3, wherein said cancerous cell is selected from the group consisting of hepatocytes, pancreatic cells, lung cells, thyroid cells, thymus cells, brain cells, neuronal cells, glial cells, skin cells, breast tissue cells, prostate tissue cells, spleen cells, muscle cells, kidney cells, and bladder cells.

See also claims 6 and 9 of related U.S. Patent No. 6,190,887, which issued with claims drawn in part to the treatment of cancer by administration of a p53 gene in a viral vector.

Applicants respectfully submit that at the time the application was filed one of ordinary skill in the art would have expected that the demonstrated methods and

compositions for enhanced delivery of the p53 gene would result in expression of a tumor suppressor gene or suicide gene in a cell *in vivo*. After all, unenhanced forms of such gene therapy using p53 was considered patentable as of a much earlier priority date.

Again, the present invention provides methods of obtaining expression of a tumor suppressor gene or a suicide gene in a cell by contacting the cell with an adenoviral vector that has a deletion of all or part of the protein IX coding region. The deletion of the protein IX region from the adenoviral vector is advantageous in that it aids in the making of adenoviral preparations that are free of contaminating vectors that arise through recombination.

As the Examiner is aware, all of the issued patents discussed above merely adhere to a standard set by the Federal Circuit when addressing pharmaceutical inventions. As noted previously, the Federal Circuit has held:

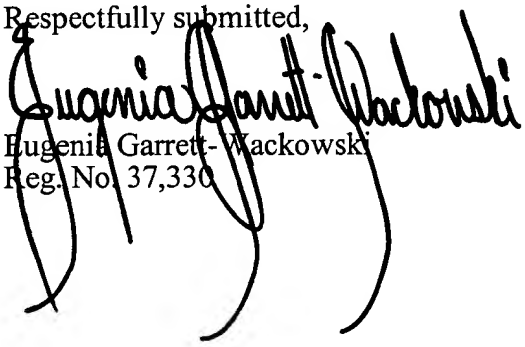
> Usefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans. Were we to require Phase II testing in order to prove utility, the associated costs would prevent many companies from obtaining patent protection on promising new inventions, thereby eliminating an incentive to pursue, through research and development, potential cures in many crucial areas such as the treatment of cancer (*In re Brana* 34 U.S.P.Q. 2nd 1436 (Fed. Cir. 1995))

Applicants request that their application be judged by the same standard as the above patents and respectfully further request that the above grounds for rejection be reconsidered and withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is urged. If the Examiner believes a telephone conference would aid in the prosecution of this case in any way, please call the undersigned at 925-472-5000.

Respectfully submitted,



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